Is poor nutrition masking the effects of depomedroxyprogesterone acetate on bones in adolescent users?

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ABSTRACT

Introduction: Research in the developed countries has documented bone loss in adolescents who use depomedroxyprogesterone acetate (DMPA) as a contraceptive for less than two years. DMPA use often begins during adolescence in Bangladesh, a South Asian developing country, where more than 50% of women are undernourished. Poor nutrition is also associated with low bone mineral density (BMD) in South Asian women. We investigated the effects of long-term (two or more years) DMPA use on BMD in Bangladeshi women who started its use in their adolescence.

Methods: Lumbar spine and femur neck BMD were acquired using dual energy X-ray absorptiometry for 100 adolescents (50 DMPA users and 50 non-users) in a cross-sectional study in Dhaka, Bangladesh. Multivariate analysis was used to determine the associations between BMD and DMPA use. Stratified analysis of DMPA use investigated the determinants of BMD in both groups.

Results: The participants (mean age 18 +/− 2 years) were generally below their ideal body weight. No significant differences in BMD were found between the two groups. Weight (odds ratio [OR] 0.96, 95 percent confidence interval [CI], 0.92–1.00) and height (OR 0.68, 95 percent CI 0.49–0.94) were independent determinants (p-value is less than 0.05) of lumbar and femur neck BMD, respectively.

Conclusion: Poor nutritional status, indicated by a less-than-ideal body weight, may be masking the effects of DMPA on bone loss among adolescent users. Our findings suggest that nutritional supplementation may be required with DMPA prescription to promote bone health in adolescent users who are approaching peak bone mass.

Keywords: adolescent women, Bangladesh, bone mineral density, depomedroxyprogesterone acetate, nutrition

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INTRODUCTION

Depomedroxyprogesterone acetate (DMPA), a female injectable progesterone-only hormonal contraceptive that is available worldwide,[1,2] (Depo-Provera®, Pfizer, New York, NY, USA) is known to decrease bone mineral density (BMD) in adolescents[1,3-5] who have yet to achieve their peak bone mass.[6-8] Despite the likelihood of recovery after discontinuation of its use,[8,9] the reported average rate of more than 3% yearly bone loss in both the lumbar and femur neck regions is alarming during the growth period in adolescence.[6,7,10] Studies showing the deleterious effects of DMPA on bones have mostly been conducted in developed countries and were also limited to monitoring BMD in adolescents with less than two years of DMPA use.[1,6,7,9,10] Thus, it has been recommended that investigations be conducted to confirm bone loss in long-term (two or more years) DMPA users and in those who started using the method before achieving their peak bone mass.[6,7,9,10] It has also been recommended that a cost-benefit assessment be carried out before DMPA is prescribed to young women.[1] Due to its effects on bones, healthcare providers in the developed world now prescribe DMPA in moderation and with caution, for use only for a limited amount of time.[8,11,12] The same rationale for cost-benefit assessment for a DMPA prescription may not be applicable in developing countries, where different social contexts require different healthcare priorities.[13] Early marriage during adolescence, playing a subordinate role in the family and poor nutrition are common experiences for women in Bangladesh,[13-15] a South Asian developing country.

DMPA is second in choice for contraception among Bangladeshi women[16] who often begin contraceptive use during adolescence.[13] About 7% of the contraception prevalence rate is attributable to DMPA use[16] in Bangladesh. More than 50% of Bangladeshi women are undernourished[15] and known to suffer from vitamin D

deficiency, which can negatively affect bone health.[17,18] Poor socioeconomic status and nutrition, indicated by a less-than-expected body weight, are associated with lower BMD in women (age 20–60 years) in Pakistan and India.[19-21] Lower BMD has also been reported in Bangladeshi women (age 30–34 years) who are using DMPA when compared to oral contraceptive pill users and non-DMPA users.[22] There is a gap in knowledge regarding the effects of DMPA use on BMD in young undernourished Bangladeshi women who started using the contraceptive in their adolescent years.

The prescription policy for DMPA use may not be as simple in Bangladesh as in the developed countries, where FDA recommendation and black box warning are used as policy guidelines.[12] Maternal choices of contraception and health over social preference in Bangladesh may not be easily comparable to those in the developed world.[13,14] Despite concerns regarding bone loss, no established policy guideline for DMPA prescription in relation to bone health in adolescent users is yet available.[4] Nevertheless, DMPA is popular among Bangladeshi adolescents who may find the concealing option of the injectable method conveniently favourable in their social settings.[13] Patient determinants, such as the nutritional status related to bone health, may also affect prescription policies for DMPA use.[23] It is therefore important to determine the indicators of BMD among long-term adolescent DMPA users, which may help in designing a prescription policy for DMPA use in this vulnerable age group.

The primary objective of this study was to determine the association between long-term DMPA use and decreased BMD in women who began their use in adolescence, compared to those (from similar age and socioeconomic group) who did not use any hormonal contraceptives. We further investigated the determinants of BMD in these two groups using separate multivariate logistic models to determine the potential risk factors for bone loss.

METHODS

A total of 100 Bangladeshi women were recruited to participate in this cross-sectional study conducted in Dhaka, Bangladesh in 2003. The participants were patients from similar socioeconomic backgrounds who were attending two reproductive health clinics run by a non-governmental organisation located in Dhaka. They were divided into DMPA users (n = 50) and non-DMPA users (n = 50), depending on their history of DMPA use. DMPA users were women who started using DMPA (150 mg intra-muscular injection every three months) at age ≤ 19 years and had been users for at least two years. Non-DMPA users were women who were not on any hormonal contraceptive methods at that time and must not have utilised hormonal contraceptives for at least six months at the time of recruitment. Women with a history of bone disease or major fractures were excluded from the study.

One of the principal investigators, who was able to speak the native language (Bengali), trained a data collector for recruitment and data collection in Dhaka. DMPA users and non-users were identified through the clinic documents. Participants were recruited over a period of six months by the data collector with help from local field workers employed by the clinic. Some participants were approached to participate in the study during their routine clinic visit; others were contacted through the field workers and were approached at the clinic at a later time. Each participant voluntarily signed an informed consent form before participating in the study. We recruited women under the age of 18 who were married, and they were therefore able to give voluntary consent. Approval to conduct the study was obtained from the Institutional Review Board of Baylor College of Medicine, Houston, TX, USA and the Bangladesh Medical Research Council.

Data on age, weight, height, monthly income (in 'taka', the Bangladeshi currency), history of contraceptive use, reproductive history (age of menarche, number of pregnancies and number of months since last childbirth), physical activities (walking to and from work for ≥ one mile each way), dairy intake (daily vs. none) and the use of calcium and vitamin supplement was obtained via a questionnaire survey. The lack of formal institutional education among our participants limited us from collecting information on education level; however, all the participants were able to sign their names. Smoking was not reported by any participant. Data on alcohol consumption, which is not a usual and culturally accepted behaviour in the community of our interest, was not collected.

Most women were unable to recall their exact age of menarche. Based on a previous report,[24] the age of 12 years was used as the average age of menarche and as a point of reference for the length of DMPA use. The participants had no difficulty reporting the number of years since they started their first period. Thus, if a woman started using DMPA six years after menarche, her age at the start of DMPA use would be 18 (12 + 6) years. The length of DMPA use was also well documented in the patient's medical record. As more than two-thirds (68%) of the users started DMPA use immediately after childbirth, we excluded the length of DMPA use from the multivariate model, and the duration of use since the last

Table I. Population characteristics of DMPA users and non-users.

Population characteristic	Mean ± SD (range)			p-value
	Total	DMPA users (n = 50)	Non-DMPA users (n = 50)	
Age (yrs)	18 ± 2 (13–21)	19 ± 1	17 ± 2	< 0.05
Weight (kg)	42 ± 7 (21–65)	42 ± 7	42 ± 6	0.76
Height (cm)	150 ± 6 (117–160)	150 ± 5	150 ± 7	0.98
BMI (kg/m^2)	19 ± 3 (9–29)	19 ± 3	19 ± 3	0.76
Monthly income*	3 ± 1 (0.6–9.0)	3 ± 1	3 ± 1	0.76
Pregnancies				
None	20	2	38	< 0.05
One	60	62	58	
Time since last childbirth (mths)	31 ± 18 (2–96)	38 ± 16 (24–96)	19 ± 15 (2–60)	< 0.05
Length of amenorrhea (mths)	8 ± 12	15 ± 14	2 ± 4	< 0.05
Do not walk at least one mile daily	12	10	14	0.76
No dairy intake	41	42	40	0.84
No calcium supplement intake	88	90	86	0.54
No multivitamin intake	77	82	72	0.24
Below average lumbar spine BMD	56	56	56	1.00
Lumbar spine BMD (g/cm^2)		0.987 ± 0.10	0.984 ± 0.11	0.87
Below average femur neck BMD	43	44	42	0.84
Femur neck BMD (g/cm^2)		0.870 ± 0.13	0.874 ± 0.12	0.88

* Income is in thousands of taka, the Bangladeshi currency.
DMPA: depomedroxyprogesterone acetate; BMI: body mass index; BMD: bone mineral density; SD: standard deviation

childbirth (a common variable for both groups) was kept in the model instead. The number of months since the last childbirth in the DMPA users thus became a surrogate for the length of time for DMPA use in the user group. Five non-DMPA users (10%) had their last childbirth less than six months ago. In the non-DMPA user group, no significant differences in BMDs (lumbar or femur neck) were detected between women whose last childbirth was < six months ago and those whose childbirth was ≥ six months ago, and therefore, all non-DMPA users were considered in the same category for the variable, "months since last child birth".

Recreational physical activities were not reported by any of our participants. However, most women walked to and from work every day. In addition, most reported engaging in manual labour for work, although the types of activities were not reported due to a lack of specific questions asked in the survey. Based on the pattern of the report, walking less than one mile each way between work and home was set as risk level for data analysis. Participants reported milk intake in different forms, for instance, "a little bit with rice or tea", or in yogurt form. None reported milk intake in terms of glasses or servings per day. Given this limitation in quantifying milk or dairy intake, we reported any kind of dairy intake as positive dairy intake per day. No dairy intake was considered risk level for our analysis.

Lumbar spine (L1–L4) BMD (LBMD) and femur neck BMD (FBMD) (g/cm^2)[25] were acquired by a Lunar DPX-L dual energy X-ray absorptiometry (DEXA) (GE Medical Lunar, Madison, WI, USA) scanner. The data collector accompanied the participants to a nearby facility to obtain their BMD measurements. The same trained technician performed the scanning on all participants. No T-score was available due to the lack of reference data for the particular age group of our participants. Participants were thus divided into two sub-groups based on their mean BMD. The group with a below-average BMD was considered to have low BMD and was used as the reference group for the multivariate analyses.

The data was analysed using the STATA software version 9.0 (StataCorp LP, College Station, TX, USA). Descriptive statistics showed the population characteristics by DMPA use: DMPA users and non-DMPA users. A general multivariate model was developed to determine the association between BMD (lumbar and femur neck regions) and DMPA use. The model was adjusted for age, weight, height, income, the number of pregnancies, the number of months since the last childbirth, physical activity, dairy intake, vitamin and calcium supplement use. Age since menarche was excluded from the multivariate model to avoid co-linearity with age. The variable "Groups", which distinguishes DMPA users from non-DMPA users, was the independent variable in this

Table II. Determinants of lumbar spine BMD in the general and stratified models according to DMPA use.

Determinant of lumbar spine BMD	Odds ratio (95% confidence interval)		
	General model	Stratified models	
		DMPA users	Non-DMPA users
Age	0.89 (0.64–1.24)	0.85 (0.47–1.54)	1.26 (0.63–2.52)
Weight	0.96 (0.92–1.00)*	0.96 (0.91–1.01)	1.00 (0.91–1.11)
Height	0.90 (0.72–1.13)	0.71 (0.47–1.07)	0.75 (0.50–1.13)
Monthly income	1.00 (0.99–1.00)	1.00 (0.99–1.00)	0.99 (0.99–1.00)
Number of pregnancies	2.36 (0.7–7.24)	3.50 (0.65–18.97)	5.27 (0.29–97.17)
Years since last childbirth	0.99 (0.97–1.03)	1.01 (1.01–1.11)*	0.91 (0.82–0.99)*
Length of amenorrhoea	1.02 (0.97–1.07)	1.02 (0.97–1.08)	1.21 (0.83–1.76)
Walk at least a mile daily	0.63 (0.16–2.46)	0.32 (0.03–3.90)	1.56 (0.06–39.18)
Dairy intake	1.52 (0.53–4.37)	0.65 (0.14–2.94)	17.25 (0.65–455.92)
Multivitamin use	0.82 (0.16–4.11)	5.87 (0.37–94.10)	0.02 (0.00–2.01)
Calcium use	1.49 (0.20–10.98)	0.98 (0.03–36.88)	3.13 (0.05–184.91)
Groups	1.00 (0.28–3.56)	-	-

* p-value < 0.05
BMD: bone mineral density; DMPA: depomedroxyprogesterone acetate

multivariate model. BMD was the outcome variable for the multivariate models. Separate general models were developed for LBMD and FBMD. The data was stratified by DMPA use to determine the indicators of BMD for DMPA users and non-DMPA users. Separate multivariate models were developed with LBMD and FBMD as dependent variables, where low BMD was the reference population for all stratified models. All the results are reported as odds ratio (OR) with 95% confidence interval (CI).

RESULTS

The mean age of the study participants (n = 100) was 18 ± 2 (range 13–21) years. They were considered underweight based on the ideal body weight (45.5 + 2.3 [height in inches – 60] kg). Both the DMPA and non-DMPA users were similar in terms of their height, weight, BMI and monthly income (Table I). DMPA users were older, had a greater number of pregnancies and a longer length of time since their last childbirth compared to the non-DMPA users (Table I). The mean length of time of DMPA use was 29 ± 7 months. There was no significant difference in BMD either in the lumbar or femur neck region between the two groups (Table I). The mean lumbar spine BMD was 0.986 ± 0.11 (range 0.729–1.242) g/cm^2 and that of the femur neck BMD was 0.872 ± 0.13 (range 0.496–1.224) g/cm^2. Despite the lack of available T-score for the particular age range of women, most participants (84%) above 19 years of age (n = 24) had a low BMD (LBMD 0.982 ± 0.09 g/cm^2, range 0.841–1.160 g/cm^2 and FBMD 0.838 ± 0.13 g/cm^2, range 0.496–1.036 g/cm^2), in terms of age-matched Z-score reported by the scanner manufacturer's database. Table I describes the population characteristics of the DMPA users and non-DMPA users.

Multivariate logistic analysis (general model) did not show any significant differences in either LBMD or FBMD between the DMPA users and non-DMPA users (Table II). Weight was an independent determinant (OR 0.96, 95% CI 0.92–1.00) of LBMD ($p < 0.05$) (Table II), while height was the independent determinant (OR 0.68, 95% CI 0.49–0.94) of FBMD ($p < 0.05$) (Table III) in the general multivariate model. Neither weight nor height remained significantly associated with LBMD in the stratified models (Table II). However, height remained significantly associated with FBMD only in DMPA users (Table III).

While the length of time since the last childbirth was not a determinant of BMD in either the lumbar or femur neck regions in the general multivariate model, the outcome changed in the stratified model, with LBMD as the dependent variable (Table II). DMPA users with a longer period of time since the last childbirth were 1.01 times more likely (OR 1.01, 95% CI 1.01–1.11) to have low LBMD ($p < 0.05$) compared to non-DMPA users, who were 9% less likely (OR 0.91, 95% CI 0.82–0.99) to have low LBMD ($p < 0.05$) (Table II). Taller DMPA users were 50% less likely (OR 0.50, 95% CI 0.28–0.89) to have low FBMD (Table III). Higher monthly income was an independent determinant of high FBMD for DMPA users (Table III).

DISCUSSION

There was no significant difference in LBMD and FBMD between the DMPA users and non-users in our study. In general, the participants had lower BMD compared to

Table III. Determinants of femur neck BMD in the general and stratified models according to DMPA use.

Determinant of femur neck BMD	Odds ratio (95% confidence interval)		
	General model	Stratified models	
		DMPA users	Non-DMPA users
Age	0.98 (0.68–1.42)	1.40 (0.70–2.78)	2.13 (0.60–7.53)
Weight	0.96 (0.92–1.01)	0.96 (0.90–1.02)	0.94 (0.80–1.10)
Height	0.68 (0.49–0.94)*	0.50 (0.28–0.89)*	0.44 (0.17–1.14)
Monthly income	1.00 (0.99–1.00)	1.00 (1.00–1.00)*	0.99 (0.99–1.00)
Number of pregnancies	3.03 (0.91–10.02)	1.90 (0.32–11.20)	19.76 (0.81–481.20)
Years since last childbirth	0.99 (0.95–1.03)	1.02 (0.97–1.07)	0.91 (0.79–1.04)
Length of amenorrhoea	1.00 (0.96–1.05)	0.99 (0.93–1.04)	1.75 (0.98–3.13
Walk at least a mile daily	0.94 (0.23–3.90)	0.50 (0.06–4.45)	3.04 (0.05–173.85)
Dairy intake	0.70 (0.23–2.13)	0.57 (0.11–2.97)	5.70 (0.15–214.71)
Multivitamin use	3.85 (0.65–22.85)	20.76 (0.88–490.07)	2.35 (0.01–602.46)
Calcium use	0.32 (0.03–3.02)	0.60 (0.01–27.54)	0.01 (0.00–15.57)
Groups	0.70 (0.18–2.71)	-	-

* p-value < 0.05

BMD: bone mineral density; DMPA: depomedroxyprogesterone acetate

their age-matched peers and other adolescent DMPA users reported previously.[26] Lower weight and height were independent determinants of low (less than average) BMD in our participants. A lower income was also associated with low (less than average) FBMD in DMPA users.

Our finding of no significant differences in BMD between DMPA uses and non-DMPA users is similar to that reported by Scholes et al in a cross-sectional study of adolescent girls (aged 14–18 years) in the United States (US), and although non-significant, a trend of lower LBMD with longer DMPA use was reported by the authors.[26] DMPA users with a longer time since their last childbirth were more likely to have low (less than average) LBMD in our study. A greater likelihood of low LBMD in DMPA users with a longer time since childbirth, a surrogate for length of DMPA use in our study, is consistent with findings from the US study.[26] Non-DMPA users with a longer time since their last childbirth were less likely to have low LBMD, which can be explained by reversible bone loss due to pregnancy and lactation.[19,21,22] The length of lactation and a greater number of pregnancies were associated with low BMD in South Asian women.[22] Although the multivariate models were adjusted for the number of pregnancies among our participants, the lack of information on birth spacing and the length of lactation limits us from determining any confounding effect from these factors on BMD in our analysis. A small sample size also prevented further investigation with stratified analysis by length of time since the last childbirth.

The positive association between lower weight and lower BMD in Pakistani and Indian women[19,21,22] was due to poor nutrition. The association of low weight and height with low BMD in our study conforms to previous findings.[19,21,22] Girls in Bangladesh were reported to have lower nutritional intake than the recommended daily allowance.[13] Vitamin D deficiency in Bangladeshi women of childbearing age[17,18] may also negatively impact their BMD. A lower-than-recommended ideal body weight in our participants indicates a need for improving the nutritional status in these women, particularly among adolescent DMPA users. Very few women in our study reported any dairy intake (Table I). Calcium and multivitamin supplement use was also very low (Table I). The lack of information on vitamin D levels and supplemental use of vitamins limits us from reporting any effect of these nutrients on the BMD. Nonetheless, our results reasonably raise the question that poor nutrition in the participants may be masking the effect of DMPA use on bone. The DMPA users, regardless of age, had a similar BMD (lumbar and femur neck) compared to the non-DMPA users. No increase in BMD with increased age adds to the World Health Organization (WHO) concern[4] that DMPA use in undernourished women may hinder the gaining of peak bone mass when DMPA is started during adolescence. Our results could be of assistance in developing an evidence-based prescription policy for adolescent DMPA users. We recommend prescribing nutritional supplements, including calcium and vitamin D, to DMPA users, specifically to those who begin its use during adolescent years.

According to a WHO report, 80% of Bangladeshi women marry in their adolescence, 50% of whom marry by the age of 15.[13] Even if contraception is practised later in marriage, for many, that would mean beginning family

planning while still in their adolescent years. About 57% of our participants had a child by the age of 19. The median birth interval in Bangladesh is 39 months, also implying interim contraception use.[13] Poor nutritional status reported with lower body weight, low dairy intake and low supplemental calcium and vitamin use may itself (without DMPA use) pose a risk for poor bone health in these women.[27] Bone loss during pregnancy and lactation[19,21] should also be considered when prescribing DMPA to undernourished adolescent women who have yet to reach their peak bone mass. Other contraceptive methods should be considered during adolescence, and this may need to be emphasised, specifically among women who are undernourished. In addition to the duration of use, an awareness campaign for healthcare providers may help focus on age and nutritional status when prescribing DMPA. A longitudinal study with nutritional intervention (e.g. calcium and vitamin D supplementation) in adolescent DMPA users may help decide on a prescription policy by confirming the effects of DMPA on undernourished adolescent bones.

Long-term DMPA use (mean length of use 29 ± 7 months) among the participants was the strength of this study. However, its cross-sectional nature limits us from following any trend of change with longer DMPA use or discontinuation. To the extent that our findings reflect the risk of bone loss in undernourished long-term DMPA users, the results from this study may be generalisable to other populations with a similar age group.

Our findings suggest that nutritional supplementation, such as calcium and vitamin D for all adolescents and specifically, for those who require DMPA prescription, should be encouraged so as to promote bone health as they approach their peak bone mass. Contrary to most studies,[6-8] no change in the BMD of adolescent DMPA users compared to those without any hormonal contraceptive use was reported in our study. However, as evidenced from the above discussion, the effect on bone from DMPA use may have been masked due to poor nutrition, which requires further investigation. It is therefore imperative that research continues to be conducted on the effects of DMPA on BMD in women who start DMPA use in adolescence, especially in developing countries whose population has similar characteristics.

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